Lucas, Z
10/722733



FILE 'REGISTRY' ENTERED AT 10:44:39 ON 21 DEC 2004
L34 312 S HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR/SQSP

FILE 'CAPLUS' ENTERED AT 10:45:37 ON 21 DEC 2004
L35 381 S L34
L36 142 S L35 AND (TREAT? OR THERAP? OR PREVENT?)
L37 23 S L36 AND (CONJUGAT? OR LINK?)

L37 ANSWER 1 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Nov 2004
ACCESSION NUMBER: 2004:927026 CAPLUS
DOCUMENT NUMBER: 141:400875
TITLE: Polyethylene glycol **linked** glucagon-like peptide-1 (GLP-1) compounds
INVENTOR(S): Dimarchi, Richard Dennis; Glaesner, Wolfgang; Millican, Rohn Lee, Jr.; Vick, Andrew Mark; Zhang, Lianshan
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004093823 | A2 | 20041104 | WO 2004-US6082 | 20040319 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-456081P P 20030319

AB The invention provides GLP-1 compds. coupled to at least one polyethylene glycol mol. or derivative thereof, resulting in a biol. active peptide with an extended half-life and a slower clearance when compared to that of un-PEGylated peptide. These PEGylated GLP-1 compds. and compns. are useful in **treating** diabetes, obesity, irritable bowel syndrome and other conditions that would be benefited by lowering plasma glucose, inhibiting gastric and/or intestinal motility and inhibiting gastric and/or intestinal emptying, or inhibiting food intake.

IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)
**123475-27-4**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyethylene glycol **linked** glucagon-like peptide-1 (GLP-1) compds.)

L37 ANSWER 2 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 30 Jul 2004
ACCESSION NUMBER: 2004:609843 CAPLUS
DOCUMENT NUMBER: 141:152200
TITLE: Recombinant production of glucagon like peptide-1 (7-36) fragment and/or GLP-1 analogs in large quantities by ligating genes in tandem
INVENTOR(S): Sun, Yukun; Wu, Dengxi; Wu, Aizhen; Zhu, Zhiyong; Yu, Gang; Zhou, Jiaxiang; Zhao, Shaoling
PATENT ASSIGNEE(S): Shanghai Hua-Yi Bio-Tech Lab., Peop. Rep. China
SOURCE: U.S. Pat. Appl. Publ., 35 pp., Cont.-in-part of Appl. No. PCT/CN02/00502.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2004146985 | A1 | 20040729 | US 2004-761717 | 20040120 |
| WO 2003016349 | A1 | 20030227 | WO 2002-CN502 | 20020717 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
WO 2002-CN502 A2 20020717
CN 2001-126278 A 20010719

AB This invention discloses a method of producing glucagon like peptide GLP-1(7-36) polypeptide or glucagon like peptide-1 analogs by ligating genes in tandem. Also disclosed are the recombinant polypeptides produced by this method. Exogenous administration of GLP-1 (7-36) or GLP-1 analogs can stimulate the secretion of insulin. The present invention provides a method, which could present a hybrid sites to ligate multiple copies of genes encoding GLP-1(7-36) or GLP-1 analogs in tandem. Expression of the resulting series-**linked** or interactively **linked** DNA fragments may yield a fusion protein containing multiple copies of GLP-1(7-36) and/or GLP-1 analogs. After cleavage of the fusion protein and further purification, large quantities of GLP-1(7-36) and/or GLP-1 analogs may then be obtained. At the 5' and 3' terminal, cleavage sites for restriction endonucleases BglII and BamHI are introduced resp., and thus complementary cohesive ends arise from restriction digestion of BglII and BamHI, which facilitate ligation of DNA fragments in tandem. The construction process to create the expression plasmid containing one copy of GLP-1 (7-36) gene is depicted.

IT **123475-27-4 123475-27-4D**, C-terminal amidated
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(amino acid sequence; recombinant production of glucagon like peptide-1 (7-36) fragment and/or GLP-1 analogs in large quantities by ligating genes in tandem)

IT **106612-94-6,** 7-37-Glucagon-like peptide I (human)
RL: PRP (Properties)
(unclaimed sequence; recombinant production of glucagon like peptide-1 (7-36) fragment and/or GLP-1 analogs in large quantities by ligating genes in tandem)

L37 ANSWER 3 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 23 Jul 2004
ACCESSION NUMBER: 2004:589280 CAPLUS
DOCUMENT NUMBER: 141:134691
TITLE: Sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders
INVENTOR(S): Wadsworth, Samuel C.; Armentano, Donna; Gregory, Richard J.; Parsons, Geoffrey
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of U.S. Ser. No. 215,272.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| US 2004143104 | A1 | 20040722 | US 2003-716326 | | 20031117 |
| US 2004002468 | A1 | 20040101 | US 2002-215272 | | 20020807 |
| PRIORITY APPLN. INFO.: | | | US 2001-310982P | P | 20010808 |
| | | | US 2002-215272 | A2 | 20020807 |

AB The invention provides sequences of a precursor glucagon-like peptide 1 (GLP-1) comprising human GLP-1 **linked** to a heterologous signal sequence. The invention also relates to a method of promoting insulin production in an individual comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1. The present invention also relates to a method of **treating** an individual having a blood sugar defect (e.g., type I or type II diabetes), comprising administering to the individual an effective amount of a nucleic acid encoding the precursor GLP-1. In a particular embodiment, the invention pertains to a method of **treating** an individual having a blood sugar defect sugar defect comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1 wherein the precursor GLP-1 comprises a signal sequence which codes for precursor cleavage at the activation cleavage site of the precursor GLP-1.

IT **123475-27-4P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GLP-1 (7-36) sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **106612-94-6P,** 7-37-Glucagon-like peptide I (human)

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human glucagon-like 1 peptide sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **498593-36-5 498593-37-6 725371-78-8 725371-79-9**
RL: PRP (Properties)
(unclaimed protein sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **498573-32-3 725250-02-2**
RL: PRP (Properties)
(unclaimed sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

L37 ANSWER 4 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 17 Jun 2004
ACCESSION NUMBER: 2004:490736 CAPLUS
DOCUMENT NUMBER: 141:47336
TITLE: Combination **treatment** for diabetes and related diseases using exendins and thiazolidinediones
INVENTOR(S): Knudsen, Lotte Bjerre
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | | DATE |
|---|---|---|---|---|---|
| WO 2004050115 | A2 | 20040617 | WO 2003-DK824 | | 20031201 |
| WO 2004050115 | A3 | 20040722 | | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW | | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | | |
| US 2004180824 | A1 | 20040916 | US 2003-726734 | | 20031203 |
| PRIORITY APPLN. INFO.: | | | DK 2002-1864 | A | 20021203 |
| | | | US 2002-431999P | P | 20021209 |

AB The invention provides methods for **treatment** and/or **prevention** of diabetes and diabetes-related diseases. More specifically, the methods and uses of the invention pertains to administration of an exendin-4 compound in combination with administration of a thiazolidinedione insulin sensitizer.

IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(exendin-thiazolidinedione combination **treatment** for diabetes and related diseases)

L37 ANSWER 5 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 19 Mar 2004
ACCESSION NUMBER: 2004:220169 CAPLUS
DOCUMENT NUMBER: 140:264513
TITLE: Polyethylene glycol-**linked** GLP-1 receptor agonists and their pharmacological methods of use
INVENTOR(S): Pan, Clark; Whelan, James P.
PATENT ASSIGNEE(S): Bayer Pharmaceuticals Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004022004 | A2 | 20040318 | WO 2003-US28093 | 20030904 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-408696P P 20020906
US 2003-439369P P 20030109

AB The invention provides modified GLP-1 receptor agonists comprising a GLP-1 receptor agonist **linked** to a polyethylene glycol polymer having a mol. weight of greater than 30 kD, as well as related formulations and dosages and methods of administration thereof for **therapeutic** purposes. More particularly, these modified GLP-1 receptor agonists, compns. and methods are useful in providing a **treatment** option for those individuals afflicted with a metabolic disorder such as diabetes and prediabetic states such as impaired glucose tolerance, and impaired fasting glucose, by inducing glucose-dependent insulin secretion, without reducing gastrointestinal motility.

IT **106612-94-6P**, 7-37-Glucagon-like peptide I (human)
**123475-27-4P**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyethylene glycol-**linked** GLP-1 receptor agonists and **therapeutic** use)

IT **672297-54-0 672297-57-3**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyethylene glycol-**linked** GLP-1 receptor agonists and

**therapeutic** use)
IT **106612-94-6D**, 7-37-Glucagon-like peptide I (human), PEG **conjugates 123475-27-4D**, PEG **conjugates 672297-54-0D**, PEG **conjugates 672297-57-3D**, PEG **conjugates**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyethylene glycol-**linked** GLP-1 receptor agonists and **therapeutic** use)

L37 ANSWER 6 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 Mar 2004
ACCESSION NUMBER: 2004:203938 CAPLUS
DOCUMENT NUMBER: 140:259049
TITLE: Transferrin fusion libraries with **therapeutic** proteins for improved serum stability
INVENTOR(S): Prior, Christopher P.; Turner, Andrew J.; Sadeghi, Homayoun
PATENT ASSIGNEE(S): Biorexis Pharmaceutical Corporation, USA
SOURCE: PCT Int. Appl., 243 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004020588 | A2 | 20040311 | WO 2003-US26779 | 20030828 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003226155 | A1 | 20031204 | US 2003-384060 | 20030310 |
| WO 2004020454 | A2 | 20040311 | WO 2003-US26742 | 20030828 |
| WO 2004020454 | A3 | 20041104 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |

| PRIORITY APPLN. INFO.: | | |
|---|---|---|
| US 2002-406977P | P | 20020830 |
| US 2003-384060 | A | 20030310 |
| US 2003-485404P | P | 20030709 |
| US 2001-315745P | P | 20010830 |

US 2001-334059P P 20011130
US 2002-231494 A2 20020830

AB Modified fusion proteins of transferrin and **therapeutic** proteins or peptides with increased serum half-life or serum stability are disclosed. Preferred fusion proteins include those modified so that the transferrin moiety exhibits no or reduced glycosylation, binding to iron or bicarbonate, and/or binding to the transferrin receptor. Thus, a fusion protein comprising modified human modified transferrin and an antifusogenic HIV-1 peptide (T-20) is made by fusing one or more copies of the nucleotide sequence encoding the peptide to the nucleotide sequence encoding modified transferrin to produce a fusion protein with a peptide fused to the N- or C-terminus of transferrin or fused internally into into modified transferrin. The fusion protein is engineered not to allow glycosylation when produced in yeast by converting the Asn-413 and Asn-611 codons to GAT and GAC by oligonucleotide-directed mutagenesis. The nucleotide sequence is also optimized for expression in Pichia pastoris. Addnl. fusions are exemplified for INGAP, peptide mimics of erythropoietin, fusogenic inhibitor peptides against Rous sarcoma virus, various cytokines, various interferons, and various single-chain antibodies. Phage display libraries comprising the fused proteins are also encompassed by this invention.

IT **669037-31-4**
RL: PRP (Properties)
(unclaimed protein sequence; transferrin fusion libraries with **therapeutic** proteins for improved serum stability)

L37 ANSWER 7 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 18 Jan 2004
ACCESSION NUMBER: 2004:41516 CAPLUS
DOCUMENT NUMBER: 140:105831
TITLE: Pharmaceutical compositions and uses of GLP-1 mimetics for the **treatment** of diabetes
INVENTOR(S): Steiness, Eva
PATENT ASSIGNEE(S): Zealand Pharma A/S, Den.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004005342 | A1 | 20040115 | WO 2003-DK463 | 20030702 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-393917P P 20020704
US 2003-465613P P 20030424

AB The present invention relates to use of GLP-1 or a related mol. having GLP-effect for the manufacture of a medicament for **preventing** or **treating** diabetes in a mammal. The amount and timing of administration of said medicament are subsequently reduced to produce a 'drug holiday'. Practice of the invention achieves effective **therapy** without continuous drug exposure and without continuous presence of **therapeutic** levels of the drug. The invention also discloses a method of **treating** diabetes and related disorders in a mammal by administering glucagon like peptide (GLP-1) or a related mol. having GLP-1 like effect and thereby providing a **therapeutically** effective amount of endogenous insulin.

IT **240481-22-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucagon-like peptide **conjugates**; pharmaceutical compns. and uses of GLP-1 mimetics for **treatment** of diabetes)

IT **87805-34-3**, Glucagon-like peptide I (human) **87805-34-3D**, Glucagon-like peptide I (human), lipophilic derivs. **99658-04-5D**, lipophilic derivs. **104364-62-7D**, Glucagon-related peptide I (guinea pig clone gpGCG-2), lipophilic derivs. **106612-94-6**, 7-37-Glucagon-like peptide I (human) **106612-94-6D**, Glucagon-like peptide I(7-37) (human), lipophilic derivs. **107444-51-9** **107444-51-9D**, lipophilic derivs. **119637-73-9** **121181-17-7**, Glucagon-like peptide 1 (Octodon degus) **121181-17-7D**, Glucagon-related peptide 1 (Octodon degus), lipophilic derivs. **123475-27-4D**, lipophilic derivs. **138324-91-1 138324-93-3 138324-94-4** **138324-95-5 138347-75-8 157569-66-9D**, lipophilic derivs. **157629-57-7D**, lipophilic derivs. **204521-54-0 204521-55-1 204656-00-8** **204656-03-1D**, lipophilic derivs. **204656-27-9** **204656-30-4D**, lipophilic derivs. **204656-35-9** **204656-36-0 204656-51-9 204656-61-1** **204656-63-3D**, lipophilic derivs. **204656-67-7D**, lipophilic derivs. **204656-74-6D**, lipophilic derivs. **204656-84-8D**, lipophilic derivs. **204996-97-4**, NNC 901167 **243857-90-1 307314-60-9 307315-09-9** **308239-12-5 308239-65-8 308240-40-6** **308240-57-5 308243-89-2 308244-15-7** **308349-07-7 308806-00-0 309729-06-4** **309729-07-5 309729-11-1 309729-12-2** **309729-42-8 309729-72-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. and uses of GLP-1 mimetics for **treatment** of diabetes)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 8 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 21 Dec 2003
ACCESSION NUMBER: 2003:991273 CAPLUS
DOCUMENT NUMBER: 140:42466
TITLE: Preparation of modified glucagon-like peptide-1 analogs
INVENTOR(S): Dimarchi, Richard Dennis; Smiley, David Lee; Zhang,

Lianshan
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003103572 | A2 | 20031218 | WO 2003-US15395 | 20030602 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-385927P P 20020604
OTHER SOURCE(S): MARPAT 140:42466
AB The invention encompasses glucagon-like peptide-1 (GLP-1) compds. containing a GLP-1 peptide or a GLP-1 peptide with an extended C-terminus that is modified with a reactive group that is capable of forming covalent bonds with a blood component to form a **conjugate**. The **conjugates** may be formed in vivo or ex vivo. Methods of **treating** a subject in need of GLP=1 receptor stimulation using these GLP-1 compds. are also disclosed. Thus, HVEGTFTSDVSSYLEEQAAKEFIAWLIKGRGK[3-(2-pyridyldithio)propanamide]amide was prepared and **conjugated** to human serum albumin. The **conjugate** was tested for in vitro potency and shown to have an EC50 value that is about the same as that of Val8-GLP-1-(7-37)OH.
IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)
RL: PRP (Properties)
(unclaimed sequence; preparation of modified glucagon-like peptide-1 analogs)

L37 ANSWER 9 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 10 Dec 2003
ACCESSION NUMBER: 2003:963032 CAPLUS
DOCUMENT NUMBER: 140:12336
TITLE: CJC-1131 ConjuChem
AUTHOR(S): Giannoukakis, Nick
CORPORATE SOURCE: Diabetes Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA
SOURCE: Current Opinion in Investigational Drugs (Thomson Current Drugs) (2003), 4(10), 1245-1249
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Current Drugs
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. ConjuChem is developing CJC-1131, a drug affinity complex

**conjugate** of glucagon-like peptide 2 for the potential **treatment** of type 2 diabetes.

IT **532951-64-7**, CJC 1131
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CJC-1131 for **treatment** of type 2 diabetes)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 10 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 07 Dec 2003
ACCESSION NUMBER: 2003:951164 CAPLUS
DOCUMENT NUMBER: 140:13719
TITLE: Methods and DNA constructs for high yield production of polypeptides by including inclusion body fusion partner (IBFP) peptide
INVENTOR(S): Xia, Yuannan; Peng, Luan
PATENT ASSIGNEE(S): Restoragen Inc., USA
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003100022 | A2 | 20031204 | WO 2003-US16645 | 20030523 |
| WO 2003100022 | A3 | 20040715 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-383212P P 20020524

AB The invention provides an inclusion body fusion partner (IBFP) to increase peptide and polypeptide production in a cell. The IBFP causes the fusion protein to form any insol. mass in a cell called an inclusion body, thus enhances isolation of the target proteins through self-adhesion, solubility, purification stability, resistance to proteolysis, or altered isoelec. point.

The invention also provides expression cassettes encoding a tandem polypeptide having a preselected polypeptide, an inclusion body fusion partner, a cleavable peptide **linker**, and a fusion tag operably **linked** in any order that will cause the tandem polypeptide to form an inclusion body. Specifically claimed is an expression cassette comprising the following operably **linked** nucleic acid sequence: 5' Pr-(TIS)D-(IBFP1)E-(CL1)G-ORF-[CL2-ORF]L-(CL3)M-(IBFP2)Q-(SSC)R-(CL4)T-(Ft)w-(Tr)X-3, wherein Pr is a promoter sequence, TIS encodes a translation initiation sequence, IBFP1 encodes a first inclusion

body fusion partner with sequence AEEEEILLEVSLVFKVKEFAPDAPLFTGPA, or a variant thereof, CL1 encodes a first cleavable peptide **linker**, ORF encodes a preselected polypeptide, CL2 encodes a second cleavable peptide **linker**, CL3 encodes a third cleavable peptide **linker**, IBFP2 encodes a second inclusion body fusion partner with above sequence or a variant thereof, SSC is a suppressable stop codon, CL4 encodes a fourth cleavable peptide **linker**, Ft encodes a fusion tag, such as T7 tag (MASMTGGQQMGRGS), and Tr is a transcription terminator sequence, wherein D or X : 0 to 4; R: 0 to 2; E, G, L, M, Q, T or W: independent 0 to 20; either one or both of IBFP1 or IBFP2 is present, and wherein expression of the expression cassette produces a tandem polypeptide that forms an inclusion body when expressed in a cell. The preselected polypeptide include bioactive and/or **therapeutic** polypeptides, such as GLP-1 (glucagon-like peptide-1), GLP-2, parathyroid hormone (PTH), growth hormone releasing factor (GRF), clostripain, or a variant thereof. Also provided are vectors expressing various fragments of GLP-1 and GRF and demonstration of their expression and purification

IT **628823-77-8 628823-79-0 628823-81-4**
RL: PRP (Properties)
(unclaimed protein sequence; methods and DNA constructs for high yield production of polypeptides by including inclusion body fusion partner (IBFP) peptide)

IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)
**123475-27-4**
RL: PRP (Properties)
(unclaimed sequence; methods and DNA constructs for high yield production of polypeptides by including inclusion body fusion partner (IBFP) peptide)

L37 ANSWER 11 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 07 Dec 2003
ACCESSION NUMBER: 2003:951163 CAPLUS
DOCUMENT NUMBER: 140:13718
TITLE: Methods and optimized DNA constructs for high yield production of polypeptides by including inclusion body fusion partner (IBFP) peptide
INVENTOR(S): Harley, Scott; Williams, James A.; Luan, Peng; Xia, Yuannan
PATENT ASSIGNEE(S): Restoragen, Inc., USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003100021 | A2 | 20031204 | WO 2003-US16643 | 20030523 |
| WO 2003100021 | A3 | 20040910 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-383370P P 20020524

AB The invention provides 15 inclusion body fusion partner (IBFP) peptides to increase peptide and polypeptide production in a cell. The IBFP causes the fusion protein to form any insol. mass in a cell called an inclusion body, thus enhances isolation of the target proteins through self-adhesion, solubility, purification stability, resistance to proteolysis, or altered isoelec. point. The invention also provides expression cassettes encoding a tandem polypeptide having a preselected polypeptide, an inclusion body fusion partner, a cleavable peptide **linker**, and a fusion tag operably **linked** in any order that will cause the tandem polypeptide to form an inclusion body. Specifically claimed is an expression cassette comprising the following operably **linked** nucleic acid sequence: 5' Pr-(TIS)D-(IBFP1)E-(CL1)G-ORF-[CL2-ORF]L-(CL3)M-(IBFP2)Q-(SSC)R-(CL4)T-(Ft)w-(Tr)X-3, wherein Pr is a promoter sequence, TIS encodes a translation initiation sequence, IBFP1 encodes a first inclusion body fusion partner, or a variant thereof, CL1 encodes a first cleavable peptide **linker**, ORF encodes a preselected polypeptide, CL2 encodes a second cleavable peptide **linker**, CL3 encodes a third cleavable peptide **linker**, IBFP2 encodes a second inclusion body fusion partner with above sequence or a variant thereof, SSC is a suppressable stop codon, CL4 encodes a fourth cleavable peptide **linker**, Ft encodes a fusion tag, such as T7 tag (MASMTGGQQMGRGS), and Tr is a transcription terminator sequence, wherein D or X : 0 to 4; R: 0 to 2; E, G, L, M, Q, T or W: independent 0 to 20; either one or both of IBFP1 or IBFP2 is present, and wherein expression of the expression cassette produces a tandem polypeptide that forms an inclusion body when expressed in a cell. The preselected polypeptide include bioactive and/or **therapeutic** polypeptides, such as GLP-1 (glucagon-like peptide-1), GLP-2, parathyroid hormone (PTH), growth hormone releasing factor (GRF), clostripain, or a variant thereof. Also provided are vectors expressing various fragments of GRF and demonstration of their expression and purification

IT **628824-89-5**
RL: PRP (Properties)
(unclaimed protein sequence; methods and optimized DNA constructs for high yield production of polypeptides by including inclusion body fusion partner (IBFP) peptide)

IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)
**123475-27-4**
RL: PRP (Properties)
(unclaimed sequence; methods and optimized DNA constructs for high yield production of polypeptides by including inclusion body fusion partner
(IBFP) peptide)

L37 ANSWER 12 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 21 Nov 2003
ACCESSION NUMBER: 2003:913280 CAPLUS
DOCUMENT NUMBER: 139:379453
TITLE: Genes showing altered patterns of expression in multiple sclerosis and their diagnostic and

**therapeutic** uses

INVENTOR(S): Dangond, Fernando; Hwang, Daehee
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003095618 | A2 | 20031120 | WO 2003-US14462 | 20030507 |
| WO 2003095618 | A3 | 20041021 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2004018522 | A1 | 20040129 | US 2003-430762 | 20030506 |
| PRIORITY APPLN. INFO.: | | | US 2002-379284P | P 20020509 |
| | | | US 2003-430762 | A1 20030506 |

AB The present invention identifies a number of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of **therapies**. In addition, these genes identify **therapeutic** targets, the modification of which may **prevent** MS development or progression. Genes were identified by determination of expression profiling. A large number of genes showing altered patterns of expression were identified, with the most discriminatory genes being those for: phosphatidylinositol transfer protein, inducible nitric oxide synthase, CIC-1 (CLCN1) muscle chloride channel protein, placental bikunin (AMBP), receptor kinase ligand LERK-3/Ephrin-A3, GATA-4, thymopoietin, transcription factor E2f-2, S-adenosylmethionine synthetase, carcinoembryonic antigen, the ret oncogene, a G protein-**linked** receptor (clone GPCR W), GTP-binding protein RALB, tyrosine kinase Syk, LERK-2/Ephrin-B1, ELK1 tyrosine kinase oncogene, transcription factor SL1, phospholipase C, gastricsin (progastricsin), and the D13S824E locus.

IT **481287-25-6**, Protein (human gene GCG)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes showing altered patterns of expression in multiple sclerosis and their diagnostic and **therapeutic** uses)

L37 ANSWER 13 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Jul 2003
ACCESSION NUMBER: 2003:571103 CAPLUS
DOCUMENT NUMBER: 139:122690

TITLE: Albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins

INVENTOR(S): Ballance, David James; Turner, Andrew John; Rosen, Craig A.; Haseltine, William A.

PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA; Delta Biotechnology Limited; Principia Pharmaceutical Corporation

SOURCE: PCT Int. Appl., 598 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003060071 | A2 | 20030724 | WO 2002-US40891 | 20021223 |
| WO 2003060071 | A3 | 20040226 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1463751 | A2 | 20041006 | EP 2002-799966 | 20021223 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 2001-341811P | P | 20011221 |
| US 2002-350358P | P | 20020124 |
| US 2002-351360P | P | 20020128 |
| US 2002-359370P | P | 20020226 |
| US 2002-360000P | P | 20020228 |
| US 2002-367500P | P | 20020327 |
| US 2002-370227P | P | 20020408 |
| US 2002-378950P | P | 20020510 |
| US 2002-382617P | P | 20020524 |
| US 2002-383123P | P | 20020528 |
| US 2002-385708P | P | 20020605 |
| US 2002-394625P | P | 20020710 |
| US 2002-398008P | P | 20020724 |
| US 2002-402131P | P | 20020809 |
| US 2002-402708P | P | 20020813 |
| US 2002-411355P | P | 20020918 |
| US 2002-411426P | P | 20020918 |
| US 2002-414984P | P | 20021002 |
| US 2002-417611P | P | 20021011 |
| US 2002-420246P | P | 20021023 |
| US 2002-423623P | P | 20021105 |
| WO 2002-US40891 | W | 20021223 |

AB The present invention encompasses albumin fusion proteins. Many **therapeutic** proteins in their native state or when recombinantly produced are typically labile mols. exhibiting short shelf-lives, particularly when formulated in aqueous solns.; fusions of the

**therapeutic** protein with human serum albumin have a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) in vitro and/or in vivo than the corresponding unfused **therapeutic** mols. Thus, albumin fusion proteins are provided comprising granulocyte colony-stimulating factor, interleukin 2, parathormone, erythropoietin, interferon β, interferon α2, interferon A/D hybrid, a single-chain insulin analog, growth hormone, and (7-36)GLP-1. Nucleic acid mols. encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Addnl. the present invention encompasses pharmaceutical compns. comprising albumin fusion proteins and methods of **treating** or **preventing** diseases, disorders or conditions related to diabetes mellitus using albumin fusion proteins of the invention.

IT **562128-10-3 562128-12-5 562128-81-8**
**562133-15-7 562133-16-8 562133-17-9**
**562133-18-0 562133-19-1 562133-20-4**
**562135-14-2 562135-16-4 562135-24-4**
**562135-28-8 562135-29-9 562135-30-2**
**562135-94-8 562135-95-9 562135-96-0**
RL: PRP (Properties)
(unclaimed protein sequence; albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins)

L37 ANSWER 14 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 25 Jul 2003
ACCESSION NUMBER: 2003:571004 CAPLUS
DOCUMENT NUMBER: 139:122689
TITLE: Albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins
INVENTOR(S): Rosen, Craig A.; Haseltine, William A.
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 1086 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003059934 | A2 | 20030724 | WO 2002-US40892 | 20021223 |
| WO 2003059934 | A3 | 20040226 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1463752 A2 20041006 EP 2002-799967 20021223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
PRIORITY APPLN. INFO.: US 2001-341811P P 20011221
US 2002-350358P P 20020124
US 2002-359370P P 20020226
US 2002-360000P P 20020228
US 2002-367500P P 20020327
US 2002-370227P P 20020408
US 2002-378950P P 20020510
US 2002-398008P P 20020724
US 2002-402131P P 20020809
US 2002-402708P P 20020813
US 2002-411355P P 20020918
US 2002-414984P P 20021002
US 2002-417611P P 20021011
US 2002-420246P P 20021023
US 2002-423623P P 20021105
WO 2002-US40892 W 20021223

AB The present invention encompasses albumin fusion proteins. Many **therapeutic** proteins in their native state or when recombinantly produced are typically labile mols. exhibiting short shelf-lives, particularly when formulated in aqueous solns.; fusions of the **therapeutic** protein with human serum albumin have a longer serum half-life and/or stabilized activity in solution (or in a pharmaceutical composition) in vitro and/or in vivo than the corresponding unfused **therapeutic** mols. Thus, albumin fusion proteins are provided comprising interferon β, interferon α2, insulin, bone morphogenetic protein 9, glucagon-like peptide-I(7-36), a hybrid interferon A/D, and extendin 4. Nucleic acid mols. encoding the albumin fusion proteins of the invention are also encompassed by the invention, as are vectors containing these nucleic acids, host cells transformed with these nucleic acids vectors, and methods of making the albumin fusion proteins of the invention and using these nucleic acids, vectors, and/or host cells. Addnl. the present invention encompasses pharmaceutical compns. comprising albumin fusion proteins and methods of **treating** or **preventing** diseases, disorders or conditions related to diabetes mellitus using albumin fusion proteins of the invention.

IT **561347-70-4P 561347-71-5P**
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; human serum albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins)

IT **107444-51-9P**, (7-36)Glucagon-like peptide 1 amide
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human serum albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins)

IT **561350-98-9 561352-52-1 561352-53-2**
**561352-54-3 561352-55-4 561352-56-5**
**561352-57-6 561353-57-9 561353-59-1**
**561353-68-2 561353-69-3 561353-70-6**
**561354-00-5 561354-01-6 561354-02-7**

RL: PRP (Properties)
(unclaimed protein sequence; albumin fusion proteins for prolonged shelf-life of **therapeutic** proteins)

L37 ANSWER 15 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 18 Mar 2003
ACCESSION NUMBER: 2003:212050 CAPLUS
DOCUMENT NUMBER: 139:1234
TITLE: Development and characterization of a glucagon-like peptide 1-albumin **conjugate**: The ability to activate the glucagon-like peptide 1 receptor in vivo
AUTHOR(S): Kim, Jung-Guk; Baggio, Laurie L.; Bridon, Dominique P.; Castaigne, Jean-Paul; Robitaille, Martin F.; Jette, Lucie; Benquet, Corinne; Drucker, Daniel J.
CORPORATE SOURCE: Banting and Best Diabetes Centre, Department of Medicine, Toronto General Hospital, University of Toronto, Toronto, ON, Can.
SOURCE: Diabetes (2003), 52(3), 751-759
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The rapid degradation of native glucagon-like peptide 1 (GLP-1) by dipeptidyl peptidase-IV (DPP-IV) has fostered new approaches for generation of degradation-resistant GLP-1 analogs. The authors examined the biol. activity of CJC-1131, a DPP-IV-resistant drug affinity complex (DAC) GLP-1 compound that **conjugates** to albumin in vivo. The CJC-1131 albumin **conjugate** bound to the GLP-1 receptor (GLP-1R) and activated cAMP formation in heterologous fibroblasts expressing a GLP-1R. CJC-1131 lowered glucose in wild-type mice, but not in GLP-1R-/- mice. Basal glucose and glycemic excursion following glucose challenge remained significantly reduced 10-12 h following a single injection of CJC-1131. Twice daily administration of CJC-1131 to db/db mice significantly reduced glycemic excursion following oral and IP glucose challenge ($P < 0.01$ to 0.05) but did not significantly lower body weight during the 4-wk study period. Levels of random fed glucose were significantly lower in CJC-1131-**treated** +/+ and db/db mice and remained significantly lower even 1 wk following discontinuation of CJC-1131 administration. CJC-1131 increased levels of pancreatic proinsulin mRNA transcripts, percent islet area, and the number of bromodeoxyuridine-pos. islet cells. These findings demonstrate that an albumin-**conjugated** DAC:GLP-1 mimics the action of native GLP-1 and represents a new approach for prolonged activation of GLP-1R signaling.
IT **532951-64-7D**, CJC 1131, albumin **conjugate**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(development and characterization of glucagon-like peptide 1-albumin **conjugate** in relation to activation of glucagon-like peptide 1 receptor in-vivo)
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 16 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 21 Feb 2003

ACCESSION NUMBER: 2003:133430 CAPLUS
DOCUMENT NUMBER: 138:180738
TITLE: Sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders
INVENTOR(S): Wadsworth, Samuel C.; Armentano, Donna; Gregory, Richard J.; Parsons, Geoffrey
PATENT ASSIGNEE(S): Genzyme Corporation, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003014318 | A2 | 20030220 | WO 2002-US25227 | 20020807 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-310982P P 20010808

AB The invention provides sequences of a precursor glucagon-like peptide 1 (GLP-1) comprising human GLP-1 **linked** to a heterologous signal sequence. The invention also relates to a method of promoting insulin production in an individual comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1. The present invention also relates to a method of **treating** an individual having a blood sugar defect (e.g., type I or type II diabetes), comprising administering to the individual an effective amount of a nucleic acid encoding the precursor GLP-1. In a particular embodiment, the invention pertains to a method of **treating** an individual having a blood sugar defect sugar defect comprising administering to the individual an effective amount of a nucleic acid encoding a precursor GLP-1 wherein the precursor GLP-1 comprises a signal sequence which codes for precursor cleavage at the activation cleavage site of the precursor GLP-1.

IT **123475-27-4P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(GLP-1 (7-36) sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **106612-94-6P**, 7-37-Glucagon-like peptide I (human)
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(human glucagon-like 1 peptide sequence; sequences of human

glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **498593-36-5 498593-37-6**
RL: PRP (Properties)
(unclaimed protein sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

IT **498573-32-3**
RL: PRP (Properties)
(unclaimed sequence; sequences of human glucagon-like 1 peptide (GLP-1) and use for **treating** diabetes and other blood sugar disorders)

L37 ANSWER 17 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 11 Oct 2002
ACCESSION NUMBER: 2002:777960 CAPLUS
DOCUMENT NUMBER: 137:293567
TITLE: Reducing the immunogenicity of fusion proteins by identifying and mutating T cell epitopes
INVENTOR(S): Gillies, Stephen D.
PATENT ASSIGNEE(S): Lexigen Pharmaceuticals Corp., USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002079232 | A2 | 20021010 | WO 2002-US9815 | 20020330 |
| WO 2002079232 | A3 | 20021212 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003166877 | A1 | 20030904 | US 2002-112582 | 20020329 |
| CA 2442363 | AA | 20021010 | CA 2002-2442363 | 20020330 |
| EP 1373301 | A2 | 20040102 | EP 2002-757870 | 20020330 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2002008207 | A | 20040928 | BR 2002-8207 | 20020330 |
| JP 2004532020 | T2 | 20041021 | JP 2002-577856 | 20020330 |
| PRIORITY APPLN. INFO.: | | | US 2001-280625P P | 20010330 |
| | | | WO 2002-US9815 W | 20020330 |

AB Disclosed are compns. and methods for producing fusion proteins with reduced immunogenicity. Fusion proteins of the invention include a junction region having an amino acid change that reduces the ability of a junctional epitope to bind to MHC Class II, thereby reducing its interaction with a T-cell receptor. Methods of the invention involve analyzing, changing, or modifying one or more amino acids in the junction

region of a fusion protein in order to identify a T-cell epitope and reduce its ability to interact with a T-cell receptor. Compns. and methods of the invention are useful in **therapy**.

IT **469356-98-7P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; reducing the immunogenicity of fusion proteins by identifying and mutating T cell epitopes)

L37 ANSWER 18 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 Jun 2002
ACCESSION NUMBER: 2002:449715 CAPLUS
DOCUMENT NUMBER: 137:28591
TITLE: Preparation of GLP-1 fusion proteins for use in **treating** diabetes mellitus and other conditions
INVENTOR(S): Glaesner, Wolfgang; Micanovic, Radmilla; Tschang, Sheng-Hung Rainbow
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 200 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002046227 | A2 | 20020613 | WO 2001-US43165 | 20011129 |
| WO 2002046227 | A3 | 20030424 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2434237 | AA | 20020613 | CA 2001-2434237 | 20011129 |
| AU 2002026897 | A5 | 20020618 | AU 2002-26897 | 20011129 |
| EP 1355942 | A2 | 20031029 | EP 2001-995845 | 20011129 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004528014 | T2 | 20040916 | JP 2002-547963 | 20011129 |
| US 2004053370 | A1 | 20040318 | US 2003-433108 | 20030529 |
| NO 2003002565 | A | 20030801 | NO 2003-2565 | 20030605 |
| PRIORITY APPLN. INFO.: | | | US 2000-251954P P | 20001207 |
| | | | WO 2001-US43165 W | 20011129 |

OTHER SOURCE(S): MARPAT 137:28591

AB The present invention relates to glucagon-like peptide-1 compds. fused to proteins that have the effect of extending the in vivo half-life of the peptides. The heterologous fusion proteins of the invention comprise a GLP-1 compound fused to human albumin, a human albumin analog or fragment,

the Fc portion of an Ig, or an analog or fragment of the Fc portion of an Ig. These fusion proteins can be used to **treat** non-insulin dependent diabetes mellitus as well as a variety of other conditions. Pharmaceutical formulations containing the fusion proteins and polynucleotides encoding the proteins are also claimed.

IT **106612-94-6**, 7-37-Glucagon-like peptide I (human)
RL: PRP (Properties)
(Unclaimed; preparation of GLP-1 fusion proteins for use in **treating** diabetes mellitus and other conditions)

IT **106612-94-6DP**, 7-37-Glucagon-like peptide I (human), analogs, fusion proteins containing **106612-94-6DP**, 7-37-Glucagon-like peptide I (human), fusion proteins containing **123475-27-4DP**, analogs, fusion proteins containing **435950-96-2DP**, fusion proteins containing
RL: BPN (Biosynthetic preparation); PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of GLP-1 fusion proteins for use in **treating** diabetes mellitus and other conditions)

L37 ANSWER 19 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 07 Feb 2001
ACCESSION NUMBER: 2001:86589 CAPLUS
DOCUMENT NUMBER: 134:157720
TITLE: Biological Activities of Glucagon-Like Peptide-1 Analogues in Vitro and in Vivo
AUTHOR(S): Xiao, Q.; Giguere, J.; Parisien, M.; Jeng, W.; St-Pierre, S. A.; Brubaker, P. L.; Wheeler, M. B.
CORPORATE SOURCE: Departments of Medicine and Physiology, University of Toronto, Toronto, ON, Can.
SOURCE: Biochemistry (2001), 40(9), 2860-2869
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Studies support a role for glucagon-like peptide 1 (GLP-1) as a potential **treatment** for diabetes. However, since GLP-1 is rapidly degraded in the circulation by cleavage at Ala2, its clin. application is limited. Hence, understanding the structure-activity of GLP-1 may lead to the development of more stable and potent analogs. In this study, we investigated GLP-1 analogs including those with N-, C-, and midchain modifications and a series of secretin-class chimeric peptides. Peptides were analyzed in CHO cells expressing the hGLP-1 receptor (R7 cells), and in vivo oral glucose tolerance tests (OGTTs) were performed after injection of the peptides in normal and diabetic (db/db) mice. [D-Ala2]GLP-1 and [Gly2]GLP-1 showed normal or relatively lower receptor binding and cAMP activation but exerted markedly enhanced abilities to reduce the glycemic response to an OGTT in vivo. Improved biol. effectiveness of [D-Ala2]GLP-1 was also observed in diabetic db/db mice. Similarly, improved biol. activity of acetyl- and hexenoic-His1-GLP-1, glucagon(1-5)-, glucagon(1-10)-, PACAP(1-5)-, VIP(1-5)-, and secretin(1-10)-GLP-1 was observed, despite normal or lower receptor binding and activation in vitro. [Ala8/11/12/16] substitutions also increased biol. activity in vivo over wtGLP-1, while C-terminal truncation of 4-12 amino acids abolished receptor binding and biol. activity. All other

modified peptides examined showed normal or decreased activity in vitro and in vivo. These results indicate that specific N- and midchain modifications to GLP-1 can increase its potency in vivo. Specifically, **linkage** of acyl-chains to the α-amino group of His1 and replacement of Ala2 result in significantly increased biol. effects of GLP-1 in vivo, likely due to decreased degradation rather than enhanced receptor interactions. Replacement of certain residues in the midchain of GLP-1 also augment biol. activity.

IT **107444-51-9,** (7-36)Glucagon-like peptide-1 amide
**154721-84-3 224638-81-7 325158-18-7**
**325158-21-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(biol. activities of glucagon-like peptide-1 analogs in vitro and in vivo)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 20 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 24 Nov 2000
ACCESSION NUMBER: 2000:824301 CAPLUS
DOCUMENT NUMBER: 134:13338
TITLE: Long lasting insulinotropic peptides
INVENTOR(S): Bridon, Dominique P.; L'Archeveque, Benoit; Ezrin, Alan M.; Holmes, Darren L.; Leblanc, Anouk; St. Pierre, Serge
PATENT ASSIGNEE(S): Conjuchem, Inc., Can.
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000069911 | A1 | 20001123 | WO 2000-US13563 | 20000517 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2363712 | AA | 20001123 | CA 2000-2363712 | 20000517 |
| CA 2373252 | AA | 20001123 | CA 2000-2373252 | 20000517 |
| WO 2000070665 | A2 | 20001123 | WO 2000-IB763 | 20000517 |
| WO 2000070665 | A3 | 20010419 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |

| | | | | | |
|---|---|---|---|---|---|
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | | |
| EP 1171582 | A2 | 20020116 | EP 2000-929748 | | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | |
| EP 1180121 | A1 | 20020220 | EP 2000-930796 | | 20000517 |
| EP 1180121 | B1 | 20031022 | | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | | |
| BR 2000010750 | A | 20020226 | BR 2000-10750 | | 20000517 |
| AU 754770 | B2 | 20021121 | AU 2000-48555 | | 20000517 |
| EP 1264840 | A1 | 20021211 | EP 2002-14617 | | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | | |
| JP 2003500341 | T2 | 20030107 | JP 2000-619018 | | 20000517 |
| JP 2003527312 | T2 | 20030916 | JP 2000-618327 | | 20000517 |
| AT 252601 | E | 20031115 | AT 2000-930796 | | 20000517 |
| PT 1180121 | T | 20040331 | PT 2000-930796 | | 20000517 |
| ES 2209885 | T3 | 20040701 | ES 2000-930796 | | 20000517 |
| US 6329336 | B1 | 20011211 | US 2000-623618 | | 20000905 |
| US 6514500 | B1 | 20030204 | US 2000-657332 | | 20000907 |
| US 2002049153 | A1 | 20020425 | US 2001-876388 | | 20010606 |
| US 6593295 | B2 | 20030715 | | | |
| ZA 2001006676 | A | 20020719 | ZA 2001-6676 | | 20010814 |
| ZA 2001009110 | A | 20020613 | ZA 2001-9110 | | 20011105 |
| NO 2001005584 | A | 20020103 | NO 2001-5584 | | 20011115 |
| US 2003108567 | A1 | 20030612 | US 2002-287892 | | 20021104 |
| US 6821949 | B2 | 20041123 | | | |
| US 2003108568 | A1 | 20030612 | US 2002-288340 | | 20021104 |
| US 2004138100 | A1 | 20040715 | US 2003-723099 | | 20031125 |
| PRIORITY APPLN. INFO.: | | | US 1999-134406P | P | 19990517 |
| | | | US 1999-159783P | P | 19991015 |
| | | | US 1999-153406P | P | 19990910 |
| | | | EP 2000-932570 | A3 | 20000517 |
| | | | WO 2000-IB763 | W | 20000517 |
| | | | WO 2000-US13563 | W | 20000517 |
| | | | US 2000-623618 | A3 | 20000905 |
| | | | US 2000-657332 | A3 | 20000907 |
| | | | US 2002-288340 | A1 | 20021104 |

AB Modified insulinotropic peptides are disclosed. The modified insulinotropic peptides are capable of forming a peptidase stabilized insulinotropic peptide. The modified insulinotropic peptides are capable of forming covalent bonds with one or more blood components to form a **conjugate**. The **conjugates** may be formed in vivo or ex vivo. The modified peptides are administered to **treat** humans with diabetes and other related diseases.

IT **87805-34-3,** Glucagon-like peptide I (human) **106612-94-6 308239-12-5 308240-40-6 308243-89-2 308349-07-7 308806-00-0 309729-06-4 309729-11-1 309729-42-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(long lasting insulinotropic peptides with antidiabetic activity)

IT **307314-60-9P 307315-09-9P 308239-65-8P**
**308240-57-5P 308244-15-7P 309729-07-5P**
**309729-12-2P 309729-72-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(long lasting insulinotropic peptides with antidiabetic activity)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 21 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 24 Nov 2000
ACCESSION NUMBER: 2000:824291 CAPLUS
DOCUMENT NUMBER: 134:21425
TITLE: Protection of endogenous **therapeutic** peptides from peptidase activity through **conjugation** to blood components
INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen
PATENT ASSIGNEE(S): Conjuchem, Inc., Can.
SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000069900 | A2 | 20001123 | WO 2000-US13576 | 20000517 |
| WO 2000069900 | A3 | 20010215 | | |
| WO 2000069900 | C2 | 20020704 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2373252 | AA | 20001123 | CA 2000-2373252 | 20000517 |
| CA 2373680 | AA | 20001123 | CA 2000-2373680 | 20000517 |
| WO 2000070665 | A2 | 20001123 | WO 2000-IB763 | 20000517 |
| WO 2000070665 | A3 | 20010419 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1105409 | A2 | 20010613 | EP 2000-936023 | 20000517 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| EP 1171582 | A2 | 20020116 | EP 2000-929748 | 20000517 |

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
EP 1264840 A1 20021211 EP 2002-14617 20000517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
JP 2003500341 T2 20030107 JP 2000-619018 20000517
JP 2003508350 T2 20030304 JP 2000-618316 20000517
AU 765753 B2 20030925 AU 2000-51393 20000517
US 6514500 B1 20030204 US 2000-657332 20000907
ZA 2001006676 A 20020719 ZA 2001-6676 20010814
ZA 2001009110 A 20020613 ZA 2001-9110 20011105
US 2003108567 A1 20030612 US 2002-287892 20021104
US 6821949 B2 20041123
US 2003108568 A1 20030612 US 2002-288340 20021104
US 2004127398 A1 20040701 US 2003-722733 20031125
US 2004138100 A1 20040715 US 2003-723099 20031125
PRIORITY APPLN. INFO.: US 1999-134406P P 19990517
US 1999-153406P P 19990910
US 1999-159783P P 19991015
EP 2000-932570 A3 20000517
WO 2000-IB763 W 20000517
WO 2000-US13576 W 20000517
US 2000-623548 A1 20000905
US 2000-657332 A3 20000907
US 2002-288340 A1 20021104

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a number of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component **conjugate**, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the peptide-blood component **conjugate** to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) **conjugated** to human serum albumin via MPA remained relatively constant through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amount of K5 in only 4 h in plasma.

IT **307314-57-4P 307314-60-9P 307315-09-9P**
**308239-65-8P 308240-25-7P 308240-57-5P**
**308242-06-0P 308244-15-7P 308244-75-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(protection of endogenous **therapeutic** peptides from peptidase activity through **conjugation** to blood components)

IT **87805-34-3**, Glucagon-like peptide I (human) **121181-17-7**, Glucagon-like peptide 1 (Octodon degus) **309257-14-5**
RL: PRP (Properties)

(unclaimed protein sequence; protection of endogenous **therapeutic** peptides from peptidase activity through **conjugation** to blood components)

IT **123475-27-4 308349-07-7**
RL: PRP (Properties)
(unclaimed sequence; protection of endogenous **therapeutic** peptides from peptidase activity through **conjugation** to blood components)

L37 ANSWER 22 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 07 Jul 2000
ACCESSION NUMBER: 2000:457193 CAPLUS
DOCUMENT NUMBER: 133:84752
TITLE: Preparation and **therapeutic** uses of PTH functional domain **conjugate** peptides, derivatives thereof, and novel tethered ligand-receptor molecules
INVENTOR(S): Gardella, Thomas J.; Kronenberg, Henry M.; Potts, John T.; Juppner, Harald
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000039278 | A2 | 20000706 | WO 1999-US31108 | 19991230 |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1147133 | A2 | 20011024 | EP 1999-968197 | 19991230 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002533115 | T2 | 20021008 | JP 2000-591171 | 19991230 |
| PRIORITY APPLN. INFO.: | | | US 1998-114577P | P 19981231 |
| | | | WO 1999-US31108 | W 19991230 |

OTHER SOURCE(S): MARPAT 133:84752
AB Novel parathyroid hormone (PTH) peptides and analogs thereof of the PTH(1-34) fragments are disclosed that combine the N-terminal signaling domain (residues 1-9) and the C-terminal binding domain (residues 15-31) via a **linker**. Nucleic acid mols. and peptides for PTH(1-9)-(Gly)5-PTH(15-31)(PG5) and PTH(1-9)-(Gly)7-PTH(15-31) and a novel PTH receptor are disclosed. Addnl., methods of screening for PTH agonists, pharmaceutical compns. and methods of **treatment** are disclosed.
IT **106612-94-6**
RL: PRP (Properties)

(unclaimed sequence; preparation and **therapeutic** uses of PTH functional domain **conjugate** peptides, derivs. thereof, and novel tethered ligand-receptor mols.)

L37 ANSWER 23 OF 23 CAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 20 Jun 1995
ACCESSION NUMBER: 1995:621604 CAPLUS
DOCUMENT NUMBER: 123:28218
TITLE: Enzymatic method for modification of recombinant polypeptides
INVENTOR(S): Wagner, Fred W.; Stout, Jay; Henriksen, Dennis; Partridge, Bruce; Manning, Shane
PATENT ASSIGNEE(S): Bionebraska, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9503405 | A2 | 19950202 | WO 1994-US8125 | 19940719 |
| WO 9503405 | A3 | 19950316 | | |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN | | | | |
| RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5512459 | A | 19960430 | US 1993-95162 | 19930720 |
| CA 2166870 | AA | 19950202 | CA 1994-2166870 | 19940719 |
| AU 9480094 | A1 | 19950220 | AU 1994-80094 | 19940719 |
| AU 693815 | B2 | 19980709 | | |
| JP 09500279 | T2 | 19970114 | JP 1994-505268 | 19940719 |
| EP 789760 | A2 | 19970820 | EP 1994-931264 | 19940719 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| US 5707826 | A | 19980113 | US 1995-470220 | 19950606 |
| US 6037143 | A | 20000314 | US 1997-967374 | 19971107 |
| US 6403361 | B1 | 20020611 | US 2000-505991 | 20000217 |

| | | | |
|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 1993-95162 | A | 19930720 |
| | WO 1994-US8125 | W | 19940719 |
| | US 1995-470220 | A3 | 19950606 |
| | US 1995-520485 | B1 | 19950829 |
| | US 1997-967374 | A1 | 19971107 |

AB An enzymic method is provided for the formation of a recombinant polypeptide which has been modified at the C-terminal end through the use of a transpeptidation process. The method is suitable for modifying recombinant polypeptides of any source including those which may be com. available, those derived from recombinant single copy or multi-copy polypeptide constructs, or those derived from single or multi-copy recombinant fusion proteins constructs. The transpeptidation reaction involves contacting an endopeptidase enzyme with a recombinant polypeptide to substitute and addition unit, of one or more acids, for leaving unit, **linked** to a core polypeptide through a cleavage site recognized by the endopeptidase enzyme. Recombinant polypeptides derived from multi-copy polypeptide constructs may be cleaved from the multi-copy

polypeptide at the N-terminal and C-terminal ends and simultaneously undergo substitution of the leaving unit by the desired addition unit. The invention utilizes known and newly discovered cleavage recognition sites of effectuate the desired modification products. Preparation of C-terminally
amidated glucagon like peptide 1 and growth hormone releasing factor using trypsin and thrombin, resp., as an endopeptidase was demonstrated.

IT **106612-94-6P 107444-51-9P 119637-73-9P**
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(glucagon like peptide 1 derivative; enzymic method for C-terminally amidation of)

E192 THROUGH E300 ASSIGNED

FILE 'REGISTRY' ENTERED AT 10:50:08 ON 21 DEC 2004

L38 109 SEA FILE=REGISTRY ABB=ON PLU=ON (106612-94-6/BI OR 123475-27-4/BI OR 107444-51-9/BI OR 87805-34-3/BI OR 121181-17-7/BI OR 307314-60-9/BI OR 307315-09-9/BI OR 308239-65-8/BI OR 308240-57-5/BI OR 308244-15-7/BI OR 308349-07-7/BI OR 119637-73-9/BI OR 308239-12-5/BI OR 308240-40-6/BI OR 308243-89-2/BI OR 308806-00-0/BI OR 309729-06-4/BI OR 309729-07-5/BI OR 309729-11-1/BI OR 309729-12-2/BI OR 309729-42-8/BI OR 309729-72-4/BI OR 498573-32-3/BI OR 498593-36-5/BI OR 498593-37-6/BI OR 532951-64-7/BI OR 672297-54-0/BI OR 672297-57-3/BI OR 104364-62-7/BI OR 138324-91-1/BI OR 138324-93-3/BI OR 138324-94-4/BI OR 138324-95-5/BI OR 138347-75-8/BI OR 154721-84-3/BI OR 157569-66-9/BI OR 157629-57-7/BI OR 204521-54-0/BI OR 204521-55-1/BI OR 204656-00-8/BI OR 204656-03-1/BI OR 204656-27-9/BI OR 204656-30-4/BI OR 204656-35-9/BI OR 204656-36-0/BI OR 204656-51-9/BI OR 204656-61-1/BI OR 204656-63-3/BI OR 204656-67-7/BI OR 204656-74-6/BI OR 204656-84-8/BI OR 204996-97-4/BI OR 224638-81-7/BI OR 240481-22-5/BI OR 243857-90-1/BI OR 307314-57-4/BI OR 308240-25-7/BI OR 308242-06-0/BI OR 308244-75-9/BI OR 309257-14-5/BI OR 325158-18-7/BI OR 325158-21-2/BI OR 435950-96-2/BI OR 469356-98-7/BI OR 481287-25-6/BI OR 561347-70-4/BI OR 561347-71-5/BI OR 561350-98-9/BI OR 561352-52-1/BI OR 561352-53-2/BI OR 561352-54-3/BI OR 561352-55-4/BI OR 561352-56-5/BI OR 561352-57-6/BI OR 561353-57-9/BI OR 561353-59-1/BI OR 561353-68-2/BI OR 561353-69-3/BI OR 561353-70-6/BI OR 561354-00-5/BI OR 561354-01-6/BI OR 561354-02-7/BI OR 562128-10-3/BI OR 562128-12-5/BI OR 562128-81-8/BI OR 562133-15-7/BI OR 562133-16-8/BI OR 562133-17-9/BI OR 562133-18-0/BI OR 562133-19-1/BI OR 562133-20-4/BI OR 562135-14-2/BI OR 562135-16-4/BI OR 562135-24-4/BI OR 562135-28-8/BI OR 562135-29-9/BI OR 562135-30-2/BI OR 562135-94-8/BI OR 562135-95-9/BI OR 562135-96-0/BI OR 628823-77-8/BI OR 628823-79-0/BI OR 628823-81-4/BI OR 628824-89-5/BI OR 669037-31-4/BI OR 725250-02-2/BI OR 725371-78-8/BI OR 725371-79-9/BI OR 99658-04-5/BI)

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(FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 10:51:13 ON 21 DEC 2004)

L39 738 S L38
L40 207 S L39 AND (TREAT? OR THERAP? OR PREVENT?)
L41 15 S L40 AND (CONJUGAT? OR LINK?)
L42 14 DUP REM L41 (1 DUPLICATE REMOVED)

L42 ANSWER 1 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.

on STN
ACCESSION NUMBER: 2004162158 EMBASE
TITLE: Degradation, receptor binding, insulin secreting and antihyperglycaemic actions of palmitate-derivatised native and Ala(8)-substituted GLP-1 analogues.
AUTHOR: Green B.D.; Gault V.A.; Mooney M.H.; Irwin N.; Harriott P.; Greer B.; Bailey C.J.; O'Harte F.P.M.; Flatt P.R.
CORPORATE SOURCE: B.D. Green, School of Biomedical Sciences, University of Ulser, Coleraine BT52 1SA, United Kingdom. b.green@ulster.ac.uk
SOURCE: Biological Chemistry, (2004) 385/2 (169-177).
Refs: 52
ISSN: 1431-6730 CODEN: BICHF3
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The hormone glucagon-like peptide-1(7-36)amide (GLP-1) is released in response to ingested nutrients and acts to promote glucose-dependent insulin secretion ensuring efficient postprandial glucose homeostasis. Unfortunately, the beneficial actions of GLP-1 which give this hormone many of the desirable properties of an antidiabetic drug are short lived due to degradation by dipeptidylpeptidase IV (DPP IV) and rapid clearance by renal filtration. In this study we have attempted to extend GLP-1 action through the attachment of palmitoyl moieties to the E-amino group in the side chain of the LyS(26) residue and to combine this modification with substitutions of the Ala (8) residue, namely Val or amino-butyric acid (Abu). In contrast to native GLP-1, which was rapidly degraded, [Lys(pal) (26)]GLP-1, [Abu(8),Lys(pal)(26)]GLP-1 and [Val(8),Lys-(pal)(26)]GLP-1 all exhibited profound stability during 12 h incubations with DPP IV and human plasma. Receptor binding affinity and the ability to increase cyclic AMP in the clonal β-cell line BRIN-BD11 were decreased by 86- to 167-fold and 15- to 62-fold, respectively compared with native GLP-1. However, insulin secretory potency tested using BRIN-BD11 cells was similar, or in the case of [Val(8),Lys(pal)(26)]GLP-1 enhanced. Furthermore, when administered in vivo together with glucose to diabetic (ob/ob) mice, [Lys(pal)(26)]GLP-1, [Abu(8),Lys(pal) (26)]GLP-1 and [Val(8),Lys(pal) (26)]GLP-1 did not demonstrate acute glucose-lowering or insulinotropic activity as observed with native GLP-1. These studies support the potential usefulness of fatty acid **linked** analogues of GLP-1 but indicate the importance of chain length for peptide kinetics and bioavailability. Copyright .COPYRGT. by Walter de Gruyter.

L42 ANSWER 2 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:424095 BIOSIS
DOCUMENT NUMBER: PREV200400421598
TITLE: Caged pancreatic islet for IDDM.
AUTHOR(S): Bae, You Han [Reprint Author]
CORPORATE SOURCE: Dept Pharmaceut and Pharmaceut Chem, Univ Utah, 421 Wakara Way,Suite 315, Salt Lake City, UT, 84108, USA you.bae@m.cc.utah.edu

SOURCE: Yonsei Medical Journal, (June 30 2004) Vol. 45, No. Suppl. S, pp. 56-60. print.
CODEN: YOMJA9. ISSN: 0513-5796.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Nov 2004
Last Updated on STN: 3 Nov 2004

AB The goals of this research are to improve the functionality (insulin secretion rate and pattern) and to expand the life-span of immunoprotected pancreatic islets. The low functionality (less than 15% of the insulin release rate of native islets in pancreas) required a large number of islets within the implant, which causes complications in surgery and discomfort for patients. The limited life-span of the islets in a biohybrid artificial pancreas (BAP) may require frequent cell reseeding and cause further supply problems in islet transplantation. Improved islet functionality and prolonged life-span will minimize the volume of the BAP by reducing the number of islets needed for diabetic patients to achieve normoglycaemia and reduce problems associated with islet supply. It is hypothesized in this research that 1) by mimicking facilitated oxygen transport in avascular tissues, the immunoprotected islets release a higher amount of insulin, recover their intrinsic bipbasic release pattern, and prolong their life-span, and 2) insulinotropic agents further promote insulin secretion from islets. Based on these hypotheses, a new BAP system will be designed which contains the water-soluble polymeric **conjugates** of oxygen carriers (or oxygen binding vehicles) and islet stimulants of sulfonylurea compounds and glucagon-like insulinotropic peptide-1 with entrapped islets in the BAP. The research examines their effects on islet viability, the amount of insulin secretion, the insulin release profile, and the life-span of immunoprotected pancreatic islets. Especially, the combined synergy effects of both hypotheses will be emphasized. The successful results in improving functionality and life-span of islets entrapped in an immunoprotected membrane can be applied in the delivery of microencapsulated **therapeutic** cells and to the miniaturization of a BAP. In addition, the approaches proposed in this research will provide a potential solution to the shortage problem of human cell or tissue sources.

L42 ANSWER 3 OF 14 EMBASE 
on STN

ACCESSION NUMBER: 2003256282 EMBASE
TITLE: Central pre-proglucagon derived peptides: Oppurtunities for **treatment** of obesity.
AUTHOR: Larsen P.J.; Vrang N.; Tang-Christensen M.
CORPORATE SOURCE: P.J. Larsen, Rheoscience, Glerupvej 2, 2610 Rodovre, Denmark. pjl@rheoscience.com
SOURCE: Current Pharmaceutical Design, (2003) 9/17 (1373-1382).
Refs: 76
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English

SUMMARY LANGUAGE: English

AB Modern societies have moved from famine to feast and obesity and its co-morbidities now sweep the world as a global epidemic. Numerous scientific laboratories and pharmaceutical companies have taken the challenge and are now exploiting novel molecular targets for **treatment** of obesity. The pre-proglucagon system constitutes interesting candidates as potential targets for new anti-obesity drugs. In the periphery, pre-proglucagon derived peptides, Glucagon-Like Peptide-1 (GLP-1), Glucagon-Like Peptide-2 (GLP-2) and oxyntomodulin (OXM) are involved in a wide variety of physiological functions, including glucose homeostasis, gastric emptying, intestinal growth, insulin secretion as well as the regulation of food intake. Peripheral administration of GLP-1 derivatives and analogues to both rodents and man have shown promising effects on food intake and body weight suggesting that such **therapies** constitute potential anti-obesity **treatment.** In the central nervous system, pre-proglucagon and hence GLP-1, GLP-2 and OXM are exclusively found in a small population of nerve cells in the nucleus of the solitary tract. These constitute a neural pathway **linking** the "viscero-sensory" brainstem to hypothalamic nuclei involved in energy homeostasis. Intracerebroventricular administration of all of the three derived peptides robustly decrease food intake. It is evident that central GLP-1 agonism probably in combination with GLP-2 and/or OXM agonism constitute a potential pharmacological tool to reduce food intake and maybe also enhance energy expenditure. This and other aspects of the current state of the role of central pre-proglucagon in energy homeostasis are reviewed.

L42 ANSWER 4 OF 14 EMBASE  on STN

ACCESSION NUMBER: 2003226161 EMBASE

TITLE: Antihypertensive effect of glucagon-like peptide 1 in Dahl salt-sensitive rats.

AUTHOR: Yu M.; Moreno C.; Hoagland K.M.; Dahly A.; Ditter K.; Mistry M.; Roman R.J.

CORPORATE SOURCE: R.J. Roman, Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, United States. rroman@mcw.edu

SOURCE: Journal of Hypertension, (1 Jun 2003) 21/6 (1125-1135). Refs: 44
ISSN: 0263-6352 CODEN: JOHYD3

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: Dahl salt-sensitive (Dahl S) rats exhibit many phenotypic traits associated with salt-sensitive hypertension in man. Specifically, they are salt-sensitive, insulin-resistant and hyperlipidemic. They also develop endothelial dysfunction, cardiac injury and glomerulosclerosis. Insulin resistance is **linked** to hypertension, renal and cardiac damage and endothelial dysfunction. Thus, an agent that has diuretic action and can improve insulin resistance, like recombinant glucagon-like peptide-1(7-36)amide (rGLP-1), may have an antihypertensive effect.

Objective: To determine whether chronic administration of rGLP-1 attenuates the development of hypertension, endothelial dysfunction and/or hypertension-induced renal and cardiac end organ damage in Dahl S rats. Methods: Mean arterial pressure (MAP) and urinary excretion of protein and albumin were measured in Dahl S rats before and after they were fed a 8% NaCl diet and infused with rGLP-1 (1 μg/kg per min, i.v.) or vehicle for 14 days. At the end of the study, the degree of renal and cardiac injury was histologically assessed and endothelium-dependent relaxing function was studied using aortic rings. In other rats, the effects of rGLP-1 on sodium and water balance and plasma glucose and insulin levels for the first 3 days following a step change in sodium intake from a 0.1% NaCl diet to 7.5 mEq/day were determined. Results: rGLP-1 significantly attenuated the development of hypertension in Dahl S rats (136 ± 7 versus 174 ± 6 mmHg). This was associated with reduction in proteinuria (46 ± 7 versus 128 ± 15 mg/day) and albuminuria (46 ± 7 versus 86 ± 18 mg/day) and improvement of endothelial function and renal and cardiac damage. rGLP-1 markedly increased urine flow and sodium excretion for the first 3 days following elevation in sodium intake. It had no significant effects on plasma glucose and insulin concentrations. Conclusion: rGLP-1 has antihypertensive and cardiac and renoprotective effects in Dahl S rats fed a high salt diet. The antihypertensive effect of rGLP-1 in Dahl S rats is due mainly to its diuretic and natriuretic effects, rather than an effect to improve insulin-resistance. 

L42 ANSWER 5 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2003147069 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12663469
TITLE: Differential activation mechanisms of Erk-1/2 and p70(S6K) by glucose in pancreatic beta-cells.
AUTHOR: Briaud Isabelle; Lingohr Melissa K; Dickson Lorna M; Wrede Christian E; Rhodes Christopher J
CORPORATE SOURCE: Pacific Northwest Research Institute, Seattle, Washington, USA.
CONTRACT NUMBER: DK 55269 (NIDDK)
DK60266 (NIDDK)
SOURCE: Diabetes, (2003 Apr) 52 (4) 974-83.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030331
Last Updated on STN: 20030520
Entered Medline: 20030519

AB Glucose can activate the mitogen-activated kinases, Erk-1/2, and the ribosomal-S6 kinase, p70(S6K), in beta-cells, contributing to an increase in mitogenesis. However, the signaling mechanism by which glucose induces Erk-1/2 and p70(S6K) phosphorylation activation is undefined. Increased glucose metabolism increases [Ca(2+)](i) and [cAMP], and it was investigated if these secondary signals were **linked** to glucose-induced Erk-1/2 and p70(S6K) activation in pancreatic beta-cells. Blocking Ca(2+) influx with verapamil, or inhibiting protein kinase A (PKA) with H89, **prevented** glucose-induced Erk-1/2 phosphorylation. Increasing cAMP levels by GLP-1 potentiated

glucose-induced Erk-1/2 phosphorylation via PKA activation. Elevation of [Ca(2+)](i) by glyburide potentiated Erk-1/2 phosphorylation, which was also inhibited by H89, suggesting increased [Ca(2+)](i) preceded PKA for glucose-induced Erk-1/2 activation. Adenoviral-mediated expression of dominant negative Ras in INS-1 cells decreased IGF-1-induced Erk-1/2 phosphorylation but had no effect on that by glucose. Collectively, our study indicates that a glucose-induced rise in [Ca(2+)](i) leads to cAMP-induced activation of PKA that acts downstream of Ras and upstream of the MAP/Erk kinase, MEK, to mediate Erk-1/2 phosphorylation via phosphorylation activation of Raf-1. In contrast, glucose-induced p70(S6K) activation, in the same beta-cells, was mediated by a distinct signaling pathway independent of Ca(2+)/cAMP, most likely via mTOR-kinase acting as an "ATP-sensor."

L42 ANSWER 6 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2003514648 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14593618
TITLE: [Gluco-incretin hormones in insulin secretion and diabetes].
Incretines, secretion d'insuline et diabete.
AUTHOR: Thorens Bernard
CORPORATE SOURCE: Institut de Physiologie, 27, rue du Bugnon, 1005 Lausanne, Suisse.. Bernard.Thorens@ipharm.unil.ch
SOURCE: Medecine sciences : M/S, (2003 Aug-Sep) 19 (8-9) 860-3.
Ref: 24
Journal code: 8710980. ISSN: 0767-0974.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200312
ENTRY DATE: Entered STN: 20031101
Last Updated on STN: 20031220
Entered Medline: 20031219

AB Nutrient ingestion triggers a complex hormonal response aimed at stimulating glucose utilization in liver, muscle and adipose tissue to minimize the raise in blood glucose levels. Insulin secretion by pancreatic beta cells plays a major role in this response. Although the beta cell secretory response is mainly controlled by blood glucose levels, gut hormones secreted in response to food intake have an important role in potentiating glucose-stimulated insulin secretion. These gluco-incretin hormones are GLP-1 (glucagon-like peptide-1) and GIP (gluco-dependent insulinotropic polypeptide). Their action on pancreatic beta cells depends on binding to specific G-coupled receptors **linked** to activation of the adenylyl cyclase pathway. In addition to their effect on insulin secretion both hormones also stimulate insulin production at the transcriptional and translational level and positively regulate beta cell mass. Because the glucose-dependent insulinotropic action of GLP-1 is preserved in type 2 diabetic patients, this peptide is now developed as a novel **therapeutic** drug for this disease.

L42 ANSWER 7 OF 14 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2003:183046 BIOSIS

DOCUMENT NUMBER: PREV200300183046
TITLE: Development and characterization of a glucagon-like peptide 1-albumin **conjugate**: The ability to activate the glucagon-like peptide 1 receptor in vivo.
AUTHOR(S): Kim, Jung-Guk; Baggio, Laurie L.; Bridon, Dominique P.; Castaigne, Jean-Paul; Robitaille, Martin F.; Jette, Lucie; Benquet, Corinne; Drucker, Daniel J. [Reprint Author]
CORPORATE SOURCE: 200 Elizabeth St., MBRW-4R-402, Toronto, ON, M5G 2C4, Canada
d.drucker@utoronto.ca
SOURCE: Diabetes, (March 2003) Vol. 52, No. 3, pp. 751-759. print.
ISSN: 0012-1797 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 9 Apr 2003
Last Updated on STN: 9 Apr 2003

AB The rapid degradation of native glucagon-like peptide 1 (GLP-1) by dipeptidyl peptidase-IV (DPP-IV) has fostered new approaches for generation of degradation-resistant GLP-1 analogues. We examined the biological activity of CJC-1131, a DPP-IV-resistant drug affinity complex (DAC) GLP-1 compound that **conjugates** to albumin in vivo. The CJC-1131 albumin **conjugate** bound to the GLP-1 receptor (GLP-1R) and activated cAMP formation in heterologous fibroblasts expressing a GLP-1R. CJC-1131 lowered glucose in wild-type mice, but not in GLP-1R-/- mice. Basal glucose and glycemic excursion following glucose challenge remained significantly reduced 10-12 h following a single injection of CJC-1131. Twice daily administration of CJC-1131 to db/db mice significantly reduced glycemic excursion following oral and IP glucose challenge ($P<0.01$ to 0.05) but did not significantly lower body weight during the 4-week study period. Levels of random fed glucose were significantly lower in CJC-1131-**treated** +/+ and db/db mice and remained significantly lower even 1 week following discontinuation of CJC-1131 administration. CJC-1131 increased levels of pancreatic proinsulin mRNA transcripts, percent islet area, and the number of bromodeoxyuridine-positive islet cells. These findings demonstrate that an albumin-**conjugated** DAC:GLP-1 mimics the action of native GLP-1 and represents a new approach for prolonged activation of GLP-1R signaling.

L42 ANSWER 8 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2001480000 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11520305
TITLE: Reduction of incretin-like salivatin in saliva from patients with type 2 diabetes and in parotid glands of streptozotocin-diabetic BALB/c mice.
AUTHOR: Kimura I; Sasamoto H; Sasamura T; Sugihara Y; Ohgaku S; Kobayashi M
CORPORATE SOURCE: Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan..
ikukokim@ms.toyama-mpu.ac.jp
SOURCE: Diabetes, obesity & metabolism, (2001 Aug) 3 (4) 254-8.
Journal code: 100883645. ISSN: 1462-8902.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20010924
Entered Medline: 20010920

AB AIM: Diabetic xerostomia is a typical syndrome in diabetic complication. We have reported that salivatin (salivary peptide P-C) derived from human saliva potentiates glucose-stimulated insulin release and inhibits arginine-stimulated glucagon release. The present study is aimed to gain further evidence on the physiological role by investigating the diabetic state-induced change in the amount of salivatin. METHODS: The amount of salivatin was measured in saliva taken from patients with type 2 diabetes with ELISA and with rabbit antiserum against human salivatin immunocytochemically in sections of parotid glands from streptozotocin-diabetic BALB/c mice. RESULTS: The amount of salivatin after a meal was reduced by diabetes in both human saliva and in the serous secretory granule of mouse parotid gland acinar cells. CONCLUSIONS: The above results suggest that salivatin lowers hyperglycaemia after meal and sustains the normal blood glucose levels by incretin-like mechanisms. The function may be damaged by diabetes, and this in turn might make the diabetes worse.

L42 ANSWER 9 OF 14 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2000333687 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10877194
TITLE: Peripheral versus central effects of glucagon-like peptide-1 receptor agonists on satiety and body weight loss in Zucker obese rats.
AUTHOR: Rodriquez de Fonseca F; Navarro M; Alvarez E; Roncero I; Chowen J A; Maestre O; Gomez R; Munoz R M; Eng J; Blazquez E
CORPORATE SOURCE: Department of Psychobiology, Faculty of Psychology, Complutense University, Madrid, Spain.
SOURCE: Metabolism: clinical and experimental, (2000 Jun) 49 (6) 709-17.
Journal code: 0375267. ISSN: 0026-0495.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200007
ENTRY DATE: Entered STN: 20000728
Last Updated on STN: 20000728
Entered Medline: 20000718

AB The present study explores the potential utility of peripheral versus central administration of glucagon-like peptide-1 (GLP-1) receptor agonists in the regulation of feeding behavior in Wistar and Zucker obese rats. Acute central (intracerebroventricular [i.c.v.]) and peripheral (subcutaneous [s.c.]) administration of both GLP-1 (7-36) amide and exendin-4 resulted in a reduction in food intake for at least 4 hours, exendin-4 being much more potent than GLP-1 (7-36) amide, especially after peripheral administration. Both Zucker obese rats (fa/fa) and their lean littermates (Fa/-) responded to acute central and peripheral administration of exendin-4. Moreover, in situ hybridization revealed specific labeling for the mRNA for GLP-1 receptors in several brain areas of both the obese and lean rats. The presence of this receptor was also

detected by affinity cross-**linking** assays. Long-term s.c. administration of exendin-4 (1 single injection per day, 1 hour prior to the onset of the dark phase of the cycle) decreased daily food intake and practically blocked weight gain in obese rats. In contrast to previous studies, these findings show that peripheral (s.c.) administration of both GLP-1 receptor agonists also induces satiety and weight loss in rats, and suggest the potential usefulness of exendin-4 as a **therapeutic** tool for the **treatment** of diabetes and/or obesity.

L42 ANSWER 10 OF 14 MEDLINE on STN
ACCESSION NUMBER: 2001073270 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11078982
TITLE: Circulating levels of incretin hormones and amylin in the fasting state and after oral glucose in GH-deficient patients before and after GH replacement: a placebo-controlled study.
AUTHOR: Jorgensen J O; Rosenfalck A M; Fisker S; Nyholm B; Fineman M S; Schmitz O; Madsbad S; Holst J J; Christiansen J S
CORPORATE SOURCE: Medical Department M (Endocrinology and Diabetes), Aarhus University Hospital, Aarhus, Denmark.. jolj@dadlnet.dk
SOURCE: European journal of endocrinology / European Federation of Endocrine Societies, (2000 Nov) 143 (5) 593-9.
Journal code: 9423848. ISSN: 0804-4643.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020125
Entered Medline: 20010103

AB OBJECTIVE: Hyperinsulinemia in association with GH excess is considered a compensatory response to insulin resistance, but the possibility of alternative insulinotropic mechanisms has not been investigated in vivo. It is also unknown how GH influences the secretion from pancreatic beta-cells of amylin, a peptide which regulates prandial glucose homeostasis and may be **linked** to development of beta-cell dysfunction. We therefore measured plasma concentrations of two gut insulinotropic hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulin-releasing peptide (GIP), and total as well as non-glycosylated amylin, in 24 GH-deficient adults before and after 4 months of GH replacement (daily evening injections of 2 IU GH/m). DESIGN: Double-blind, placebo-controlled, parallel study. METHODS: All participants underwent an oral glucose tolerance test (OGTT) at 0 and 4 months. RESULTS: A 33% suppression of fasting GLP-1 concentrations was measured in the GH group at 4 months (P=0.02), whereas a non-significant increase occurred in the placebo group (P=0.08). Fasting levels of GIP and amylin did not change significantly after 4 months in either group. The incremental response in GLP-1 during the OGTT was significantly lower after GH **treatment** as compared with both baseline (P=0.02) and the response in the placebo group (P=0. 03). The stimulation of GIP secretion following OGTT was similar on all occasions. The OGTT-induced incremental response in non-glycosylated amylin was moderately elevated

after GH **treatment** as compared with placebo (P=0.05). Plasma concentrations of glucose and insulin, both in the fasting state and after the OGTT, were higher after GH **treatment**, but the ratio between amylin and insulin remained unchanged. CONCLUSIONS: GH-induced hyperinsulinemia is accompanied by proportionate elevations in amylin concentrations and a blunting of gut GLP-1 secretion. The mechanisms underlying the suppression of GLP-1 remain to be elucidated.

L42 ANSWER 11 OF 14 EMBASE 
on STN

ACCESSION NUMBER: 1998370375 EMBASE
TITLE: Normalization of fasting glycaemia by intravenous GLP-1 ([7-36 amide] or [7-37]) in type 2 diabetic patients.
AUTHOR: Nauck M.A.; Weber I.; Bach I.; Richter S.; Orskov C.; Holst J.J.; Schmiegel W.
CORPORATE SOURCE: Prof. M.A. Nauck, Medizinische Universitatsklinik, Knappschafts-Krankenhaus, In der Schornau 23-25, 44892 Bochum, Germany. nauck.bochum@+-online.de
SOURCE: Diabetic Medicine, (1998) 15/11 (937-945).
Refs: 41
ISSN: 0742-3071 CODEN: DIMEEV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Intravenous GLP-1 [7-36 amide] can normalize fasting hyperglycaemia in Type 2 diabetic patients. Whether GLP-1 [7-37] has similar effects and how quickly plasma glucose concentrations revert to hyperglycaemia after stopping GLP-1 is not known. Therefore, 8 patients with Type 2 diabetes (5 female, 3 male; 65 ± 6 years; BMI 34.3 ± 7.9 kg m-2; HbA(1c) 9.6 ± 1.2 %; **treatment** with diet alone (n = 2), sulphonylurea (n = 5), metformin (n = 1)) were examined twice in randomized order. GLP-1 [7-36 amide] or [7-37] (1 pmol kg-1min-1) were infused intravenously over 4 h in fasted subjects. Plasma glucose (glucose-oxidase), insulin and C-peptide (ELISA) was measured during infusion and for 4 h thereafter. Indirect calorimetry was performed. Fasting hyperglycaemia was 11.7 ± 0.9 [7-36 amide] and 11.3 ± 0.9 mmol l-1 [7- 37]. GLP-1 infusions stimulated insulin secretion approximately 3-fold (insulin peak 168 ± 32 and 156 ± 47 pmol l-1, p < 0.0001 vs basal; C- peptide peak 2.32 ± 0.28 and 2.34 ± 0.43 nmol l-1, p < 0.0001, respectively, with GLP-1 [7-36 amide] and [7-37]). Four hours of GLP-1 infusion reduced plasma glucose (4.8 ± 0.4 and 4.6 ± 0.3 mmol l-1, p < 0.0001 vs basal values), and it remained in the non-diabetic fasting range after a further 4 h (5.1 ± 0.4 and 5.3 ± 0.4 mmol l-1, for GLP [7-36 amide] and [7-37], respectively). There were no significant differences between GLP-1 [7-36 amide] and [7-37] (glucose, p = 0.99; insulin, p = 0.99; C-peptide, p = 0.99). Neither glucose oxidation nor lipid oxidation (or any other parameters determined by indirect calorimetry) changed during or after the administration of exogenous GLP-1. In conclusion, GLP-1 [7-36 amide] and [7-37] normalize fasting hyperglycaemia in Type 2 diabetic patients. Diabetes **therapy** (diet, sulphonyl ureas or metformin) does not appear to influence this effect. In fasting and resting patients, the effect persists during administration of GLP-1 and for at least 4 h

thereafter, without rebound. Significant changes in circulating substrate concentrations (e.g. glucose) are not accompanied by changes in intracellular substrate metabolism.

L42 ANSWER 12 OF 14 MEDLINE on STN
ACCESSION NUMBER: 95023403 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7937345
TITLE: Glycosylation of the GLP-1 receptor is a prerequisite for regular receptor function.
AUTHOR: Goke R; Just R; Lankat-Buttgereit B; Goke B
CORPORATE SOURCE: Department of Internal Medicine, Philipps-University of Marburg, Germany.
SOURCE: Peptides, (1994) 15 (4) 675-81.
Journal code: 8008690. ISSN: 0196-9781.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19990129
Entered Medline: 19941122

AB The GLP-1 receptor on RINm5F cells is a glycoprotein with a M(r) of 63,000. **Treatment** of the receptor with glycopeptidase F generated a protein with a M(r) of 51,000, indicating that the GLP-1 receptor contains N-**linked** glycans. Tunicamycin pretreatment concentration-dependently decreased GLP-1 binding to RINm5F cells due to a decreased receptor number without change of receptor affinity. Tunicamycin exerted no effect on the GLP-1 receptor mRNA expression. The stimulation of cAMP production was decreased in tunicamycin-**treated** cells. Our data show that glycosylation of the GLP-1 receptor is a precondition for regular receptor function.

L42 ANSWER 13 OF 14 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 94200252 EMBASE
DOCUMENT NUMBER: 1994200252
TITLE: [Secondary failure with oral antidiabetic agents: What kind of **treatment**?].
L'ECHEC SECONDAIRE DES ANTI-DIABETIQUES ORAUX: POSSIBILITES **THERAPEUTIQUES**.
AUTHOR: Blanc M.H.; Galtier-Dereure F.; Parer-Richard C.; Bringer J.; Jaffiol C.
CORPORATE SOURCE: Service d'Endocrinologie, CHU Lapeyronie,F 34059 Montpellier Cedex, France
SOURCE: Revue Francaise d'Endocrinologie Clinique - Nutrition et Metabolisme, (1994) 35/2 (125-136).
ISSN: 0048-8062 CODEN: RECNAS
COUNTRY: France
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: French; English

AB Secondary failure to **treatment** with oral antidiabetic agents

(OAA) involves annually between 3 and 10% of type II non insulin **treated** diabetic patients. The progressive degradation of the glycemic control is best explained by the concept of 'glucotoxicity' **linking** chronic hyperglycemia with insulin resistance and decreased insulin secretion. A short term strict glycemic control achieved with intravenous insulin perfusion allows about 50% of the patients in failure to resume their **treatment** with OAA. A low carbohydrate diet given at the same time may be also of some help. The success of this kind of **treatment** is however not predictable by any clinical or biochemical criteria. New drugs like vanadate or IGF-1 are under investigation.

L42 ANSWER 14 OF 14 MEDLINE on STN
ACCESSION NUMBER: 83017096 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6750831
TITLE: Gastrointestinal peptides--role in pathophysiology and disease.
AUTHOR: Creutzfeldt W
SOURCE: Scandinavian journal of gastroenterology. Supplement, (1982) 77 7-20. Ref: 72
Journal code: 0437034. ISSN: 0085-5928.
PUB. COUNTRY: Norway
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198212
ENTRY DATE: Entered STN: 19900317
Last Updated on STN: 19980206
Entered Medline: 19821202

AB Progress in gut hormone research has considerably increased our knowledge in gastrointestinal physiology. However, this knowledge has not yet helped the understanding of common gastrointestinal diseases. A pathophysiological role of gut hormones has been established only for rare conditions This is because the clinical significance of the gut hormones is difficult to evaluate. Morphological and biochemical methods used in classical endocrinology can rarely be applied to gastrointestinal endocrinology because of the special design of the gut hormone system. Also gut hormones and autonomous nervous system overlap in their function. A defect of one system can be compensated by the other. Since the hormone-producing cells of the gut are stimulated by food ingestion, any functional or organic change of the digestive tract will alter gut hormone response. Accordingly, most changes of gut hormone levels are secondary. In some--apparently rare--instances such secondary changes contribute to the symptomatology of a pathological condition. In other instances gut hormone abnormalities mimic common diseases, thus demonstrating the heterogenecity of these conditions. More specific and reliable methods are needed to prove or to exclude the participation of gastrointestinal peptides in the pathogenesis of gastrointestinal disease. Gut peptides are an important **link** between nutrient entry and metabolism. This is realized by a hormonal gut factor (incretin) which augments glucose-induced insulin release. GIP is the most thoroughly investigated but not the only incretin. In addition, GIP seems to have direct effects on lipid metabolism. This would explain why fat releases more GIP than glucose. Except in the case of the metabolic hormones insulin and glucagon the **therapeutic** usefulness of gastrointestinal peptides

has not yet been established.

FILE 'HOME' ENTERED AT 10:52:29 ON 21 DEC 2004